Prospective Observational Study of Incidence and Preventable Burden of Childhood Tuberculosis, Kenya

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Prospective data on childhood tuberculosis (TB) incidence and case detection rates (CDRs) are scant, and the preventable burden of childhood TB has not been measured in prospective studies. We investigated 2,042 children (<15 years of age) with suspected TB by using enhanced surveillance and linked hospital, demographic, notification, and verbal autopsy data to estimate the incidence, CDR, risk factors, and preventable burden of TB among children in Kenya. Estimated TB incidence was 53 cases/100,000 children/year locally and 95 cases/100,000 children/year nationally. The estimated CDR was 0.20–0.35. Among children <5 years of age, 49% of cases were attributable to a known household contact with TB. This study provides much needed empiric data on TB CDRs in children to inform national and global incidence estimates. Moreover, our findings indicate that nearly half of TB cases in young children might be prevented by implementing existing guidelines for TB contact tracing and chemoprophylaxis.

Substantial progress has been made in the fight against tuberculosis (TB); however, new approaches are needed to achieve the current target set by the World Health Organization (WHO) to reduce TB incidence to 90% of 2016 levels by 2035 (*1*). A key element of WHO's End TB Strategy is the prioritization of preventive treatment (*2*). However, the preventable burden of childhood TB has not been quantified in prospective epidemiologic studies, and globally, only an estimated 7% of eligible children received isoniazid chemoprophylaxis in 2015 (*1*).

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Diagnosis of TB is more challenging in children than in adults (*3*). In low-resource settings, where TB burden is highest, diagnosis often relies on poorly validated clinical algorithms (*4*). As a result, adequate surveillance data are lacking, and published estimates of the global childhood TB burden vary widely (*1*,*5*–*11*). High-quality prospective data on the TB burden and case detection rate (CDR) in children are recognized priorities (*8*,*11*,*12*), and population-level data showing the preventable burden of childhood TB might reinforce the public health case for chemoprophylaxis in children. We designed the Kilifi Improving Diagnosis and Surveillance of Childhood TB (KIDS TB) Study to estimate the incidence, CDR, risk factors, and preventable burden of childhood TB in Kenya.

Methods

Study Sites

The study took place at Coast Provincial General Hospital (CPGH) and Kilifi County Hospital (KCH) in Coast Province, Kenya. CPGH provides primary and secondary care to the city of Mombasa and tertiary services for Coast Province. KCH is nested within the Kilifi Health and Demographic Surveillance System (KHDSS) (*13*), which covers a predominantly rural area of 891 km^2 that in March 2011 was home to 261,919 residents in 29,970 households; two thirds of pediatric admissions to KCH during the study period were derived from this system. Three other health facilities in the KHDSS provide TB smear microscopy; 12 clinics are designated TB treatment centers (Figure 1). Because of resource constraints, contact tracing was not routine and isoniazid chemoprophylaxis not available at the time of the study, despite the inclusion of these steps in national TB guidelines.

[1]The following members of the Kilifi Improving Diagnosis and Surveillance of Childhood TB (KIDS TB) Study Group also contributed to patient recruitment, investigation, and management: Victor Bandika, Jay Berkley, Kath Maitland, Susan Morpeth, Daisy Mugo, Robert Musyimi, Agnes Mutiso, John Paul Odhiambo, Monica Toroitich, and Hemed Twahir.

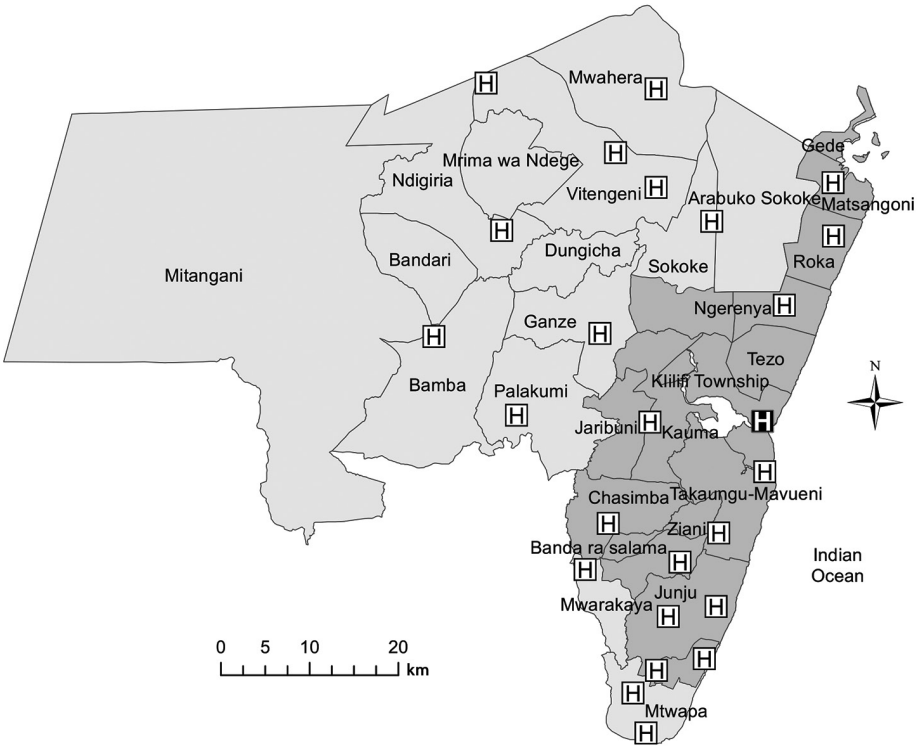

Figure 1. Kilifi District and the Kilifi Health and Demographic Surveillance Survey area (darker gray shading), showing administrative districts, Kilifi County Hospital (black square), and other tuberculosis treatment facilities (white squares), Kenya, 2010.

Participants

We established a system of enhanced passive and active childhood TB surveillance. In the passive case–detection arm, we prospectively recruited all children <15 years of age who were seen at KCH or CPGH during August 2009–July 2011 for an unexplained persistent cough for >2 weeks, pneumonia not responding to antibiotics, unexplained fever for >2 weeks, unexplained progressive weight loss or failure to thrive for >4 weeks, close contact with a person with TB, or clinical suspicion of TB for any other reason. Study clinicians and clinicians from the hospital and surrounding clinics were trained in the symptoms and signs of a range of TB presentations (online Technical Appendix Table 1, https://wwwnc.cdc.gov/EID/article/24/3/17-0785-Techapp1.pdf). We excluded children with an established alternative diagnosis that explained all the clinical features as well as children already on TB treatment for >2 weeks at presentation. In the active case–detection arm, we recruited KHDSS-resident children <5 years of age sharing a household with persons with new cases of smear-positive pulmonary TB.

Clinical Procedures

All children underwent a similar structured history and examination, chest radiography, and tuberculin skin testing according to WHO guidelines (*14*) (online Technical Appendix). Children who were able to expectorate provided up to 3 spontaneous sputum samples. Sputum induction was performed on the remainder (*14*). Further investigations including extrapulmonary or repeat sputum sampling were performed at the discretion of the clinical team caring for the patient. Provider-initiated testing and counseling for HIV was performed according to national guidelines.

We classified children as having confirmed TB, highly probable TB, possible TB, or not TB (TB excluded) according to clinical, radiologic, and microbiological findings, based closely on stringent published definitions (online Technical Appendix Table 2) (*15*,*16*). For comparison, we also applied other published clinical definitions to our dataset (online Technical Appendix). Treatment protocols followed national guidelines. Children were followed up for 6 months or until a diagnosis of TB could be confidently excluded.

Laboratory Methods

Acid-fast bacilli microscopy and mycobacterial culture using the BACTEC MGIT system (BD Diagnostics, Sparks, MD, USA) were performed according to standard protocols (*17*). Positive cultures were further characterized using the BD MGIT TBc Identification Test (BD Diagnostics) and Hain Genotype line probe assays (Hain Lifescience GmbH, Nehren, Germany), including isoniazid and rifampin drug-susceptibility testing. We performed the Xpert MTB/RIF assay version G4 (Cepheid, Sunnyvale, CA, USA) at the end of the study on specimens from all children treated for confirmed, highly probable, or possible TB as well as from children for whom a TB diagnosis had been excluded. Laboratory procedures were externally

monitored using the United Kingdom National External Quality Assessment Service's quality-assurance scheme (http://ukneqas.org.uk).

Statistical Analysis

Incidence Estimates

We used clinical data from KCH and event data from KHDSS to compile for every KHDSS-resident child a series of chronological time-span records representing the periods between consecutive birth, migration, enumeration, hospital presentation, or death events during the study period. We split these periods of observation by age category and estimated crude TB incidence rates as the total number of new TB cases identified (by both active and passive case detection) divided by the total person-years of observation in each age stratum. We compared estimates generated using the study case definitions with incidence estimates derived by applying other published clinical definitions of childhood TB to our dataset (online Technical Appendix).

Estimating the CDR

Crude incidence estimates assume all incident cases among KHDSS residents are captured by the study; however, hospital-based surveillance of childhood illnesses is known to be insensitive in this setting (*18–20*). We defined the CDR as the proportion of KHDSS-resident TB cases captured by the study. Because the actual number of children with TB is unknown, we used 3 different methods to estimate the CDR independently (detailed description in online Technical Appendix).

TB Notification Data

We linked clinical data with National Tuberculosis Programme notification data and KHDSS census data. We estimated the CDR as 1) the proportion of KHDSS-resident smear-positive childhood TB cases reported to the National Tuberculosis Programme that were captured by passive case detection at KCH, and 2) the proportion of children's household contacts of new smear-positive pulmonary TB cases captured by active contact tracing.

Hospital-Based Mortality Surveillance

We linked KHDSS vital status data with KCH admission data. We then calculated the proportion of all childhood deaths in the KHDSS area captured at KCH during the study period.

Verbal Autopsy

By using disease-specific mortality data from a contemporaneous verbal autopsy study of all deaths within the KHDSS (*21*), we estimated the proportion of childhood TB deaths captured by our study. Because the number of child TB cases diagnosed by verbal autopsy is small and healthcare-seeking behavior is usually determined by clinical features rather than diagnosis per se (*20*,*22*), we also estimated the CDR as the proportion of children who died having clinical features of suspected TB that were captured by the study.

To derive the most conservative estimates of the actual annual incidence of childhood TB, we divided crude incidence rates by the highest CDR estimate. We modeled the likely number of incident confirmed or highly probable TB (CHPTB) cases among children nationally by multiplying the total number of adult cases reported in Kenya in 2010 (*23*) by the ratio of child-to-adult cases in the KHDSS, assuming a similar ratio and adult CDR nationally. We then used denominator population data from the national census (*24*) to estimate the national incidence of childhood TB.

Risk Factors for Childhood TB

We explored risk factors for childhood TB in a nested case–control analysis of children with CHPTB (cases) and children for whom TB was excluded (controls). To mitigate ascertainment bias in analysis of TB contact history, we excluded the small minority of children identified through active contact tracing. For each association, we derived crude odds ratios (ORs) and 95% CIs. We then included in a multivariable logistic regression model those variables with at least a weak association with TB in the univariable analysis (likelihood ratio test; $p \leq 0.1$) and presented adjusted ORs and 95% CIs.

By using the number of KHDSS-resident adult cases reported to the National Tuberculosis Programme during the study period and the mean number of close contacts <5 years of age per case (*25*), we estimated the prevalence of household exposure to a person with confirmed TB among KHDSS-resident children <5 years of age. Using the contact status of CHPTB cases detected in the study, the child years at risk derived from the KHDSS census, and the exposure prevalence, we estimated the incidence of TB among contacts and noncontacts. The population attributable fraction for contact with a person with confirmed TB was calculated from the ensuing incidence rate ratio (IRR) and the exposure prevalence (p) by calculating $p(IRR - 1)/1 + p(IRR - 1)$ (online Technical Appendix).

Results

We identified 2,183 children with suspected TB during the study period and summarized patient enrollment and diagnostic assignments (Figure 2). We excluded 141 (6%) children who died, were discharged, or were lost to follow-up before their diagnostic workups, including specimen collection for mycobacterial culture, could be completed (Figure 2). We summarized baseline clinical characteristics of the remaining 2,042 children included in the analyses (Table 1).

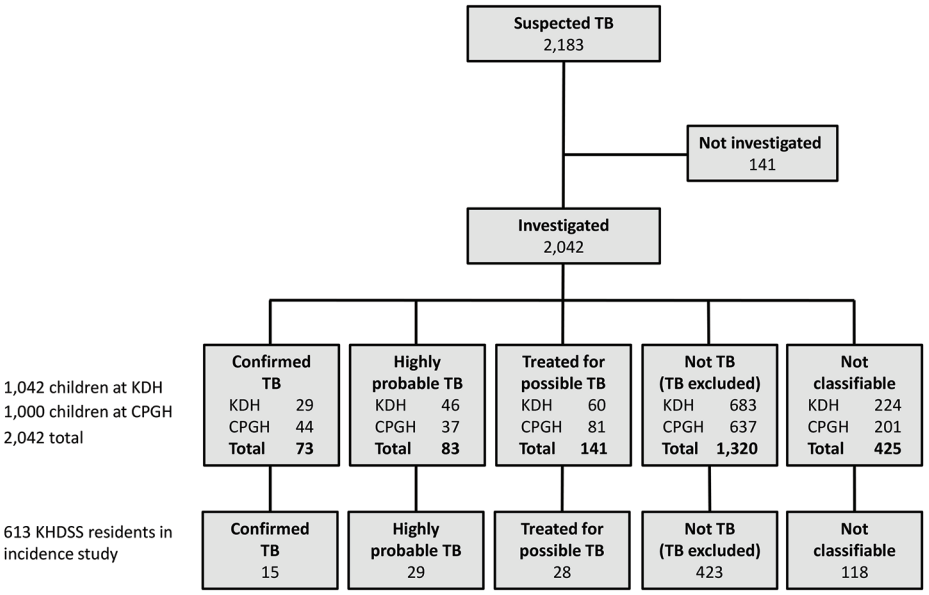

Figure 2. TB patient enrollment and disease classifications, Kilifi Health and Demographic Surveillance Survey, Kenya, August 2009–July 2011. A total of 141 children were not investigated (27 died, 40 were discharged, 3 were transferred, 1 self-discharged before workup completed, 30 defaulted outpatient follow-up, 40 had no reason documented). At KDH, 108/1,042 (10%) children investigated were identified through active contact tracing (2 confirmed TB, 4 highly probable TB, 87 not TB, 15 not classifiable). CPGH, Coast Provincial General Hospital; KDH, Kilifi District Hospital; KHDSS, Kilifi Health and Demographic Surveillance Survey; TB, tuberculosis.

Crude Incidence Estimates

We determined crude, hospital-based, age-specific incidence rates based on the study definitions (Table 2). The incidence of all childhood TB was 30.2 (95% CI 23.6–38.0) cases/100,000 children/year. The incidence of CHPTB was 18.4 (95% CI 13.4–24.7) cases/100,000 children/year; this estimate was very similar to that derived by retrospectively applying to our data consensus definitions of definite or probable TB that were published after completion of our study (*26*) (20.5 [95% CI 15.2–27.1]/100,000/year). Both figures are at the lower end of the range of estimates derived using published clinical definitions, which vary >30-fold (2.9–91.7/100,000/year) (Table 3).

CDR and Adjusted Incidence Estimates

CDR estimates derived using TB notifications, KHDSS census data, and verbal autopsy ranged from 0.2 to 0.35 (Table 4), substantially lower than the estimated CDR of 0.82 for adults in Kenya (*41*). Hospital-based mortality surveillance provided the largest and most precise estimate of the CDR (0.35 [95% CI 0.31–0.40]), so we used this to derive the most conservative estimates of the actual community incidence of childhood TB (Table 5). After adjustment for CDR, the incidence of CHPTB and all TB among children in the KHDSS was 53 (95% CI 38–71) and 86 (95% CI 67–109) cases/100,000/year, respectively.

Implications for the National Incidence of Childhood TB

During August 2009–July 2011, a total of 678 new cases of adult TB were reported to the National Tuberculosis Programme, and an estimated 126 new CHPTB cases were reported in children (Table 5) among KHDSS residents. Nationally 89,883 adult and 5,721 child TB cases were reported in 2010 (*41*) among a population that includes ≈17.6 million children <15 years of age (*24*). Applying the ratio of adult-to-child TB cases in the KHDSS to the national caseload yields an estimated 16,704 new CHPTB cases among children <15 years of age nationally in 2010, suggesting a national childhood TB CDR of 29% and incidence of 95 cases/100,000 children/year (online Technical Appendix Table 3).

Risk Factors for Childhood TB

We summarized associations of CHPTB and important putative risk factors (Table 6). A history of known close TB contact at presentation was strongly associated with CHPTB, with an effect gradient according to the contacts' smear status, proximity, relationship, and number (online Technical Appendix Table 4). No child case-patients with a close TB contact had received isoniazid chemoprophylaxis. We observed a weaker association with HIV and in young children with severe malnutrition but no association between the presence of a bacillus Calmette-Guérin (BCG) vaccination scar and TB, although power to detect an effect was low because of the small proportion of children without a BCG vaccination scar.

Preventable TB Burden among Child Household TB Contacts

Among KHDSS-resident children <5 years of age, an estimated 1,259 were close contacts of adults with new TB cases reported during the study period. The incidence of CHPTB was 596 cases/100,000/year among children with a close TB contact and 17 cases/100,000/year among those without a close TB contact, yielding a 49% population attributable fraction for having a recent and known TB contact (online Technical Appendix Table 5).

Table 1. Baseline characteristics of children with and without TB examined at Kilifi County Hospital and Coast Provincial General Hospital, Kenya, August 2009–July 2011*

Characteristic	Confirmed TB, n = 73	Highly probable TB, n = 83	Treated for possible TB, n = 141	Not TB/TB excluded, n = 1,320	Not classifiable, n = 425
Case ascertainment					
Passive case detection	71 (97)	79 (95)	141 (100)	1,237 (94)	410 (96)
Active case detection (contact tracing)	2 (3)	4 (5)	0 (0)	83 (6)	15 (4)
Patient demographics					
Median age (interquartile range), mo	52 (16–114)	32 (13–70)	17 (10–64)	17 (10–41)	17 (9–44)
0–4 y	38 (55)	59 (71)	99 (70)	1,119 (85)	345 (81)
5–9 y	17 (25)	15 (18)	27 (19)	140 (11)	56 (13)
10–14 y	18 (25)	9 (11)	15 (11)	61 (4)	24 (6)
Sex					
M	39 (53)	43 (52)	70 (50)	696 (53)	224 (53)
F	32 (47)	40 (48)	71 (50)	624 (47)	201 (47)
Risk factors for TB					
HIV infected	17 (23)	21 (25)	42 (30)	160 (12)	112 (26)
Severely malnourished	30 (41)	37 (45)	58 (41)	457 (35)	162 (38)
BCG vaccination scar	65 (89)	86 (71)	128 (91)	1,172 (89)	338 (80)
Close TB contact	36 (49)	33 (40)	27 (19)	246 (19)	78 (18)
Clinical features of suspected TB					
Cough >2 wks	48 (66)	48 (58)	95 (67)	572 (43)	225 (53)
Fever >2 wks	45 (62)	30 (36)	92 (65)	502 (38)	196 (46)
Weight loss or failure to thrive >4 wks	42 (58)	39 (47)	77 (55)	575 (44)	208 (49)
Pneumonia not responding to 1st-line ABX	27 (37)	25 (30)	42 (30)	308 (23)	159 (37)
TB clinical syndrome					
Smear-positive pulmonary TB	20 (27)	4 (5)	0	NA	NA
Smear-negative pulmonary TB	40 (55)	69 (83)	108 (77)	NA	NA
All pulmonary TB†	60 (82)	73 (88)	108 (77)	NA	NA
Extrapulmonary TB†	30 (41)	17 (20)	46 (33)	NA	NA
Miliary TB	6 (8)	3 (4)	5 (4)	NA	NA
TB meningitis	8 (11)	2 (2)	12 (9)	NA	NA
Pleural TB	6 (9)	2 (2)	7 (5)	NA	NA
TB lymphadenitis	6 (8)	6 (7)	6 (4)	NA	NA
Osteoarticular TB	2 (3)	3 (4)	1 (1)	NA	NA
Abdominal TB	9 (12)	2 (2)	10 (7)	NA	NA
Persistent fever without a focus	0	1 (1)	13 (9)	NA	NA
Drug resistance					
Isoniazid monoresistance	0	NA	NA	NA	NA
Multidrug-resistant TB	1 (1.4)	NA	NA	NA	NA

*Values are no. (%) unless otherwise indicated. ABX, antibiotics; BCG, bacillus Calmette-Guérin; NA, not applicable; TB, tuberculosis.
†Some children had >1 focus of infection, including some with pulmonary TB and extrapulmonary TB. Among children with confirmed TB, microbiologic confirmation was required from ≥1 site; diagnosis of other sites of disease was based on the definitions of highly probable TB (online Technical Appendix Table 1, https://wwwnc.cdc.gov/EID/article/24/3/17-0785-Techapp1.pdf).

Discussion

This study provides rare prospective empiric data on the TB incidence and CDR among children <15 years of age in Kenya, a country with a high TB burden, and is one of few prospective incidence studies globally (*3*). This community-based study was nested in a demographic surveillance survey, underpinned by enhanced active and passive surveillance, mycobacterial culture facilities, and linked hospital, demographic, notification, and verbal autopsy data. We used a hierarchical diagnostic classification in keeping with recommendations for childhood TB surveillance and research (*26*,*35*). A comprehensive algorithm of clinical, radiologic, and laboratory investigations combined with careful follow-up of children enrolled in the KIDS TB Study ensured diagnostic classifications were optimized within the limitations of currently available diagnostic tools.

Although the diagnosis of confirmed TB has the highest specificity, the poor sensitivity of mycobacterial culture for childhood TB diagnosis means that incidence estimates based only on confirmed cases will underestimate the actual disease burden. Conversely, including possible TB cases in the numerator might overestimate incidence. Most children in the highly probable TB group probably did have TB, given the stringent diagnostic criteria, and although the sensitivity of this classification is not perfect, it probably captured many of the actual cases of active TB for which culture confirmation was not obtained. We therefore used a combination of confirmed or highly probable TB (CHPTB) as the measure most likely to optimize sensitivity and specificity for estimation of childhood TB incidence.

Compared with estimates based on published clinical definitions, our measure of CHPTB incidence is among the most conservative, similar to the estimate obtained by

Table 2. Crude hospital-based childhood TB incidence, by age group and diagnostic classification, Kilifi Health and Demographic Surveillance Survey, Kenya, August 2009–July 2011*

TB classification	Age group, y	No. person-years of observation	No. KHDSS-resident TB cases	Incidence, cases/100,000 children/y (95% CI)
Confirmed TB	0–4	89,503	7	7.8 (3.1–16.1)
	5–9	79,170	6	7.6 (2.8–16.5)
	10–14	70,073	2	2.9 (0.3–10.3)
	Total	238,746	15	6.3 (3.5–10.4)
Confirmed or highly probable TB	0–4	89,503	30	33.5 (22.6–47.9)
	5–9	79,170	11	13.9 (6.9–24.9)
	10–14	70,073	3	4.3 (0.9–12.5)
	Total	238,746	44	18.4 (13.4–24.7)
All TB	0–4	89,503	46	51.4 (37.6–68.6)
	5–9	79,170	21	26.5 (16.4–40.6)
	10–14	70,073	5	7.1 (2.3–16.7)
	Total	238,746	72	30.2 (23.6–38.0)

*KDHSS, Kilifi Health and Demographic Surveillance Survey; TB, tuberculosis.

retrospectively applying more recent consensus definitions for research (*26*). Even after inclusion of all TB cases, our measure remained among the lowest, suggesting that many published clinical definitions would overdiagnose TB in this and similar settings were they to be applied routinely in clinical practice. The huge range in incidence estimates derived using different case definitions emphasizes the difficulty in interpreting existing disease burden data and the need for high-quality prospective incidence studies to improve disease burden estimates.

Robust community incidence estimates depend on high-quality diagnosis to minimize misclassification as well as a high CDR. Broad screening criteria for all children admitted to hospital with any features of suspected TB, plus active case detection through contact tracing, ensured that case ascertainment at KCH was optimized. Nevertheless, the social, financial, and geographic barriers to obtaining hospital care in this setting mean that many ill KHDSS-resident children are not seen at KCH (*18–20*). Furthermore, challenges in childhood TB diagnosis, combined with limited diagnostic resources, make surveillance data from other health facilities unreliable. We therefore estimated the CDR of hospital-based surveillance at KCH by using 3 independent techniques. Each measure is necessarily a surrogate, and each has limitations, but the similarity of these estimates supports their validity.

Because we used the highest CDR estimate to generate conservative estimates of childhood TB incidence, the

Table 3. Incidence of childhood TB derived by applying other published clinical definitions, algorithms, and guidelines, in order of increasing incidence, Kilifi Health and Demographic Surveillance Survey, Kenya, August 2009–July 2011*

Author, year (reference)	Outcomes defined	No. cases	Incidence, cases/100,000 children/y (95% CI)†
WHO, 2006 (*27*)	(a) Strongly suggestive of TB‡	7	2.9 (1.2–6.0)
Stegen (*28*)	(a) Probable TB	18	7.5 (4.5–11.9)
Nair (*29*)	(a) "TB appears unquestionable"	28	11.7 (7.8–17.0)
WHO, 2006 (*27*)	(b) Requires investigation for TB‡	33	13.8 (9.5–19.4)
Graham (*26*)	Probable TB	42	17.6 (12.7–23.8)
Hawkridge (*30*)	Probable TB	54	22.6 (17.0–29.5)
Nair (*29*)	(b) TB probable or "unquestionable"	55	23.0 (17.4–30.0)
Stoltz (*31*)	Probable TB	73	30.6 (24.0–38.5)
Jeena (*32*)	Probable TB	107	44.8 (36.7–54.2)
Edwards (*33*)	Criteria for TB treatment	110	46.1 (37.9–55.5)
Ghidey (*34*)	(a) Criteria for TB treatment§	113	47.3 (39.0–56.9)
WHO, 1983 (*35*)	Probable TB	116	48.6 (40.2–58.3)
Ramachandran (*36*)	Criteria for TB treatment	118	49.4 (40.9–59.2)
Ghidey (*34*)	(b) Criteria for TB treatment§	130	54.5 (45.4–64.7)
Stegen (*28*)	(b) Probable or possible TB	136	57.0 (47.8–67.4)
Graham (*26*)	Probable or possible TB	145	60.7 (51.3–71.5)
Osborne (*37*)	Probable TB	159	66.6 (56.7–77.8)
Fourie (*38*)	High probability of TB¶	162	67.9 (57.8–79.2)
Cundall (*39*)	Probable TB	207	86.7 (75.3–99.4)
Kiwanuka (*40*)	Probable TB	219	91.7 (80.0–104.7)

*TB, tuberculosis; WHO, World Health Organization.
†Denominator for incidence calculations is the total person-years observation among children age <15 y (N = 238,746).
‡Results shown separately for (a) children whose clinical features "strongly suggest a diagnosis of TB" according to the guidelines, and (b) using broader criteria that included under "physical signs highly suggestive of TB" all the other "suggestive clinical signs" listed as requiring investigation for TB.
§Results for Ghidey and Habte tool (*34*) shown using both (a) ≥3 and (b) ≥2 signs and symptoms to define a "suggestive symptom complex of TB" (online Technical Appendix Table 1, https://wwwnc.cdc.gov/EID/article/24/3/17-0785-Techapp1.pdf).
¶For the purposes of our analyses, we used "score 2" proposed by Fourie et al (*38*), which was derived in high TB burden settings in South Africa, Madagascar, and Nicaragua.

Table 4. Case detection rate estimates derived by using TB notifications, Kilifi Health and Demographic Surveillance Survey census data, and verbal autopsy methods, Kenya, August 2009–July 2011*

Method	Calculation of CDR estimate	CDR estimate (95% CI)
TB notifications		
Passive case detection	$\frac{\text{No. KHDSS-resident smear-positive child TB cases captured by KIDS TB Study}}{\text{Total no. KHDSS-resident smear-positive child TB cases}} = \frac{3}{10}$	0.30 (0.07–0.65)
Active contact tracing	$\frac{\text{No. index cases captured at KCH}}{\text{Total no. index cases}} \times \frac{\text{No. eligible child contacts investigated}}{\text{Total no. eligible child contacts identified at KCH}} = \frac{195}{362} \times \frac{108}{297}$	0.20 (0.13–0.26)
KHDSS census		
Mortality surveillance	$\frac{\text{No. KHDSS-resident children who died at KCH}}{\text{Total no. childhood deaths among KHDSS residents}} = \frac{182}{514}$	0.35 (0.31–0.40)
Verbal autopsy		
TB deaths	$\frac{\text{No. TB deaths in VA study that occurred in children captured by KIDS TB Study}}{\text{No. TB deaths in VA study}} = \frac{2}{10}$	0.20 (0.03– 0.56)
TB suspected deaths	$\frac{\text{No. TB suspected deaths in VA study that were captured by KIDS TB Study}}{\text{No. TB suspected deaths in VA study}} = \frac{x}{y}$	0.22 (0.15–0.32)

*CDR, case detection rate; KCH, Kilifi County Hospital; KHDSS, Kilifi Health and Demographic Surveillance Survey; TB, tuberculosis, VA, verbal autopsy.

projected national incidence was 3 times higher than that reported. Nevertheless, the projected ratio of adult-to-child TB cases is still consistent with other studies in Africa (*43*,*44*) and with recent global estimates (*1*,*5*,*6*,*9*), although lower than some regional and global figures (*3*). Other estimates of the global TB burden have indicated a lower proportion of childhood cases (*7*,*8*). However, in the absence of data from children, those estimates assume a similar CDR for adults (*8*) or impute missing data based on reported proportions of smear-negative and extrapulmonary TB by age group (*7*), assumptions that have been challenged (*11*,*45*). Our study provides important empirical data on the probable CDR among children. The results suggest that the CDR among children is substantially lower than among adults and support estimates derived using other modeling approaches (*5*,*6*), including recently revised WHO estimates of global childhood TB incidence that assume a CDR of 36% (*9*).

The strong association of childhood TB with a history of close TB contact has 2 important implications for clinical practice and public health policy. First, eliciting a history of TB contact should be a standard part of the assessment of every ill child in TB-endemic settings. Among inpatients in our study, 1 in 5 with a known close TB contact had CHPTB. Early identification and investigation of this high-risk group might improve clinical outcomes through earlier diagnosis and treatment.

Second, and most important, our finding that 49% TB cases among children <5 years of age were attributable to a known household TB contact suggests that half the CHPTB cases in young children might have been prevented by chemoprophylaxis. Estimating the population attributable fraction of contact with a person with confirmed TB provides a novel approach for assessing the potential impact of TB chemoprophylaxis at the population level that might be applied to other settings. Our results from Kenya support recent global estimates of TB burden among child TB contacts (*25*). By demonstrating a large potential impact on childhood TB incidence, our findings provide further strong endorsement for existing policy recommendations for TB chemoprophylaxis (*25*,*46*).

Extrapolation of results from a single district must be interpreted with caution. Childhood TB incidence and the contribution of childhood TB cases to the total TB burden are likely to be affected by factors that vary geographically,

Table 5. Estimated annual caseload and incidence of childhood TB after adjustment for the case detection rate, Kilifi Health and Demographic Surveillance Survey, August 2009–July 2011*

TB classification	Age group, y	No. cases	Adjusted incidence, cases/100,000 children/y (95% CI)
Confirmed TB	0–4	20	22 (9–46)
	5–9	17	22 (8–47)
	10–14	6	9 (1–29)
	Total	43	18 (10–30)
Confirmed or highly probable TB	0–4	86	96 (65–137)
	5–9	31	39 (20–71)
	10–14	9	13 (3–36)
	Total	126	53 (38–71)
All TB	0–4	131	146 (107–196)
	5–9	60	76 (47–116)
	10–14	14	20 (7–48)
	Total	205	86 (67–109)

*To generate the most conservative estimates of community childhood TB incidence, we used the highest case detection rate estimate of 0.35 derived from hospital-based mortality surveillance. TB, tuberculosis.

Table 6. Crude and adjusted odds ratios for risk factors associated with confirmed or highly probable TB among children examined at Kilifi County Hospital and Coast Provincial General Hospital, Kenya, August 2009–July 2011*

	Cases		Controls					
Age group	Factor present	Factor absent	Factor present	Factor absent	Crude OR for TB (95% CI)	p value	aOR for TB (95% CI)	p value
Children <5 y								
HIV infection†	17	73	112	872	1.8 (1.0–3.2)	0.036	1.3 (0.7–2.4)	0.321
Severe malnutrition‡	56	35	413	620	2.4 (1.5–3.7)	<0.001	2.6 (1.6–4.1)	<0.001
BCG vaccination scar	82	9	921	112	1.1 (0.5–2.3)	0.779	–	
Close TB contact	33	58	125	908	4.1 (2.6–6.6)	<0.001	5.1 (3.1–8.3)	<0.001
Children 5–14 y								
HIV infection†	21	38	47	143	1.7 (0.9–3.2)	0.103	1.5 (0.8–2.9)	0.229
Severe malnutrition‡	9	50	43	157	0.7 (0.3–1.4)	0.294	–	
BCG vaccination scar	48	11	173	27	0.7 (0.3–1.5)	0.327	–	
Close TB contact	30	29	34	166	5.1 (2.6–9.9)	<0.001	5.2 (2.7–9.8)	<0.001
All children <15 y								
HIV infection†	38	111	159	1,015	2.2 (1.5–3.3)	<0.001	1.9 (1.2–2.9)	0.003
Severe malnutrition‡	65	85	456	777	1.3 (0.9–1.8)	0.130	–	
BCG vaccination scar	130	20	1,094	139	0.8 (0.5–1.4)	0.455	–	
Close TB contact	63	87	159	1,074	5.0 (3.4–7.3)	<0.001	5.0 (3.4–7.2)	<0.001

*aOR, adjusted odds ratio; BCG, bacillus Calmette-Guérin; OR, odds ratio; TB, tuberculosis.
†HIV status was missing for 1/150 (0.7%) cases and 59/1233 (4.8%) controls.
‡Severe malnutrition defined according to World Health Organization guidelines as weight-for-age z-score of ≤3 or the presence of nutritional edema (*42*).

including community TB prevalence; social and demographic factors, such as urbanization, that affect the annual risk for TB infection; prevalence of host factors, such as BCG vaccination, HIV infection, and malnutrition; and local population structures. Therefore, we did not attempt simply to age-standardize the Kilifi incidence rates to the national population of children in Kenya.

We reasoned instead that the proportion of the total TB caseload accounted for by children is probably less prone to geographic variation, and estimated the national burden of childhood TB by assuming that the CDR among adults and the ratio of adult-to-child cases is the same in the KHDSS and nationally. Importantly, the age structures of the KHDSS and Kenya are very similar (*13*,*24*), suggesting that age is unlikely to confound this approach. Compared with Kilifi, the higher estimate of TB incidence nationally is consistent with greater urbanization (*13*,*24*) and a higher annual risk for TB infection (*47*), HIV prevalence (*24*), and overall TB incidence (*1*). Because ecologic data suggest that the pediatric proportion of cases actually increases with increasing overall TB incidence (*6*,*12*), this approach might underestimate the actual national childhood TB burden. Our restriction of TB cases to those that met the stringent criteria of CHPTB and our adjustment of hospital-based incidence rates using the highest CDR estimate also suggest that our estimates are conservative.

In conclusion, by using a combination of clinical, laboratory, and epidemiologic resources not usually available for routine surveillance, we have estimated the incidence of childhood TB in Kenya. Although this study is very resource-intensive, the wide range of incidence estimates based on existing clinical definitions highlights the difficulty in interpreting routine notification data and reinforces the need for similar studies in a range of different epidemiologic settings. In a setting where routine facilities for childhood TB diagnosis are typical of most countries with a high TB burden, our results also provide important empirical data on the TB CDR among children. The results support recently improved WHO estimates of global childhood TB incidence based on modeling approaches, which assume a very similar CDR (*1*,*9*). Our findings also reinforce the urgent need to improve case detection among children to reduce childhood TB mortality (*48*). Crucially, they suggest that half the TB cases in young children might be prevented by implementing existing WHO guidelines for contact tracing and chemoprophylaxis.

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Author contributions: A.J.B., J.A.G.S., and M.L. designed the study with input from C.R.J.N., T.N.W., C.N., E.B., J.S., and K.P. A.J.B., J.L., C.M., and J.W. recruited and followed up children with suspected TB. Chest radiographs were read and interpreted by A.J.B., J.S., and K.P. A.J.B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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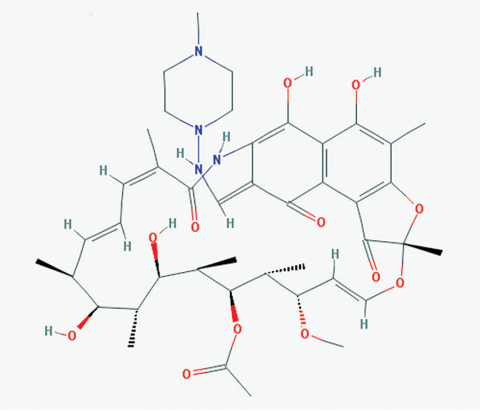
etymologia

Ronnie Henry

Rifampin *[rif-am'pin]*

In 1957, Piero Sensi and colleagues isolated a new bacterium, *Streptomyces mediterranei* (now *Amycolatopsis rifamycinica*), from a soil sample from a pine forest in France. Material extracted from fermentation broths of *A. rifamycinica* contained microbiologically active substances that, as a group, were nicknamed Rififi. *Rififi* (French slang for "trouble") was a 1955 French gangster film that was popular at the time and became the root of the name "rifamycin" for this group of antimicrobial agents. (Similarly, matamycin was originally nicknamed Mata Hari.) Rifampin (also known as rifampicin) is the N-amino-N′-methylpiperazine (AMP) derivative of rifamycin.



Chemical structure of Rifampin. Data deposited in or computed by PubChem, source: PubChem; https://pubchem.ncbi.nlm.nih.gov/compound/5381226#section=2D-Structure

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Prospective Observational Study of Incidence and Preventable Burden of Childhood Tuberculosis, Kenya

Technical Appendix

Investigation of Children Enrolled through Passive Case Detection at KCH

All children who presented to KCH with clinical features of suspected TB were weighed and underwent a structured history and examination, including questions about any history of known TB contact at the time of presentation. Tuberculin skin testing (TST) was performed using the Mantoux method and 2 tuberculin units (TU) of tuberculin PPD RT23 (*1*). A positive TST was defined as a diameter of induration ≥10mm, or ≥5mm in HIV infected or severely malnourished children (*1*). Children admitted to KCH also had a full blood count (FBC; Beckman/Coulter, Fullerton, UK), thick and thin blood films for malaria parasites (malaria parasite slide, MPS), and a blood culture (BACTEC PedsPlus, Becton Dickinson, CA, USA). Provider initiated testing and counseling (PiTC) for HIV was performed according to Kenyan national guidelines, which recommend testing for all inpatients and for all patients investigated for TB, on an opt-out basis (*2*,*3*).

All children had a posterior-anterior (PA) or anterior-posterior (AP) chest x-ray (CXR). Lateral CXRs were performed at the discretion of the clinician after reviewing the PA/AP CXR, for example to assess further any suspected hilar lymphadenopathy. CXRs were read independently by the study clinician (AJB) and by a pediatric radiologist (JS) blinded to the clinical details. Data were entered onto a standardized reporting form closely based on consensus guidelines (*4*). Discrepancies between these two readers were resolved by a second pediatric radiologist (KP) also blinded to both the clinical details and the findings of the first two readers.

Other blood tests and more specialist investigations (e.g., imaging) were performed at the discretion of the clinical team caring for the child.

Investigation of Children Enrolled through Active Contact Tracing

New cases of smear positive pulmonary TB resident within the Kilifi Health and Demographic Surveillance System (KHDSS) were identified in the KCH TB outpatient clinic, and child household contacts of these index cases identified on the KHDSS population register. For pragmatic reasons, and in keeping with Kenyan national guidelines, contact tracing focused on children under 5 years of age resident in the same household as a case of smear positive pulmonary TB, as smear positive cases are the most infectious and young children are most vulnerable to developing active TB following infection (*5*). Each index case was then invited to bring all children under 5 years in the household (symptomatic or asymptomatic) to the pediatric TB outpatient clinic for further assessment, and given sufficient money to cover the return fare to hospital.

All children identified through active contact tracing underwent a structured history and examination, anthropometry, CXR, and a TST. Those with symptoms or signs of possible TB (Technical Appendix Box 2), an abnormal CXR, or a positive TST were further investigated for suspected TB as described below.

Specimen Collection for Mycobacteriology

Appropriate clinical specimens were collected for AFB microscopy and mycobacterial culture from all children with suspected TB. Children who were able to expectorate provided three spontaneous sputum samples. Sputum induction was performed on the remainder. If sputum induction was contraindicated (e.g., due to severe respiratory distress), gastric aspiration was performed. Sputum induction and gastric aspiration were performed according to international recommendations (*6*). Further investigations including fine needle aspiration (FNA) of lymph nodes, mycobacterial culture of CSF, urine, pleural/ascitic/joint fluid, or biopsy material, or repeat sampling, were performed at the discretion of the clinical team caring for the patient according to clinical indications in individual cases. Specimens were transported to the laboratory at 2–8°C and processed the same day.

Supplementary Statistical Methods

Application of Published Clinical Diagnostic Tools to Estimate Childhood TB Incidence

To compare crude incidence estimates generated using the study case definitions with incidence estimates derived using other published clinical definitions we included clinical diagnostic tools published in the peer reviewed medical literature, and guidelines from the WHO and Kenya National TB Programme. We excluded published tools that failed to present diagnostic criteria in sufficient detail to apply them to the dataset. For those tools that included a category of confirmed TB based on microbiological diagnosis we confined our analysis to categories defined by clinical criteria alone, to explore their performance under normal programmatic conditions with limited availability of mycobacterial culture. We also retrospectively applied new consensus definitions for childhood TB research that were published after completion of our study (*4*), and derived incidence estimates for the consensus definitions of both Definite and Probable TB to facilitate comparison with future studies.

We created variables for each diagnostic score and/or diagnostic categories with close reference to the published definitions of each variable. In instances where the exact definition of a clinical variable was not clearly specified in the original publication we chose what we judged to be the most likely intended definition for application in the relevant setting and reported the definition we used. Thus 'unexplained fever' was defined as a fever for >14 days in the absence of malaria parasitaemia or evidence of focal infection; a cutoff of at least 1 week's duration was used for a history of night sweats; and 'bulky lymphadenopathy' was defined pragmatically as the presence of lymph nodes sufficiently large to perform a fine needle aspirate (usually ≥2cm diameter). 'Malnutrition not responding to treatment' was defined as death, or failure to regain 10% bodyweight (in the case of marasmus) or failure of edema to resolve (kwashiorkor), in a child admitted with severe malnutrition.

A 'suggestive symptom complex of TB' was included in the Ghidey-Habte diagnostic tool (*7*) but only vaguely defined as "*non-specific symptoms such as fever, night sweats and loss of weight, and specific symptoms related to the site invaded, e.g. cough, swelling of lymph nodes, abdominal distension, difficulty in walking, etc* ". For the purposes of our analysis we included in this definition fever, cough, night sweats, and weight loss (each for at least 2 weeks), bulky lymphadenopathy, signs of pleural effusion or ascites, gibbus, and a change in temperament or

reduced level of consciousness. We then compared incidence estimates using a requirement for either ≥2 or ≥3 of these clinical features to define a 'suggestive symptom complex of TB'.

In keeping with published definitions (*4,8,9*), a 'suggestive CXR' for TB was defined as the presence of a Ghon focus or complex, miliary infiltrate, cavities, or a pleural or pericardial effusion - unless an alternative definition was clearly presented for a particular clinical tool in which case the definition presented was used.

Using each of these published clinical definitions we calculated TB incidence using as the numerator the number of KHDSS-resident children fulfilling each definition during the study period.

Estimating the Case Detection Rate

Using TB Notification Data

We linked National Tuberculosis Programme (NTP) notification data with KHDSS census data to estimate the CDR in both the passive and the active case detection arms of the study.

Passive Case Detection

We used notification data from the Kilifi District TB Register to estimate the proportions of KHDSS resident child TB cases captured at KCH through passive case detection. Data from the register were double entered into a bespoke electronic database using Filemaker Pro version 10 (Filemaker Inc, CA, USA). The KHDSS residence status (resident or non-resident) of each patient in the register was then coded manually by a senior demographer with several years of local experience and detailed knowledge of the KHDSS area (CN), using the address documented in the register. All KHDSS resident childhood TB cases notified between August 2009 and July 2011 were identified from this database. We then manually cross-referenced the name, age and treatment date of each of these cases against the KIDS TB Study database to identify children that had also been captured by passive case detection at KCH. To limit disease misclassification among young children we limited the analysis to smear positive cases, and calculated the case detection rate as:

$$CDR = \frac{\text{No. KHDSS resident, smear-positive child TB cases captured by the KIDS TB Study}}{\text{Total no. KHDSS resident smear-positive child TB cases}}$$

Active Case Detection

Case ascertainment of children aged 0 to 4 years in the active (contact tracing) case detection arm depended first on identification of all KHDSS resident cases of smear positive pulmonary TB; and second on each of these smear positive index cases bringing their child household contacts to the pediatric TB clinic for investigation. By linking smear and residence data from the Kilifi District TB Register with data from our register of all smear positive pulmonary TB patients seen in the KCH TB clinic we determined the proportion of all notified smear positive pulmonary TB cases from the KHDSS area that were captured at KCH. We identified from the KHDSS census the number of child household contacts under 5 years old for each index case, and thereby the total number of eligible child household contacts under 5 years old and resident in the KHDSS area. We assumed that the average number of child household contacts was similar among index cases who presented to KCH and elsewhere, and that the risk of TB among contacts was independent of where the index case presented or whether the child was brought to the pediatric TB clinic for investigation. The case detection rate in the active case detection arm was then calculated as:

$$CDR = \frac{\text{No. index cases captured at KCH}}{\text{Total no. index cases}} \times \frac{\text{No. eligible child contacts investigated}}{\text{Total no. eligible child contacts identified at KCH}}$$

We derived 95% confidence intervals based on the variance of the product of these two proportions using standard methods.

Using Hospital-Based Mortality Surveillance

We used the unique personal identification number (PID) of each KHDSS resident child to link vital status data from KHDSS census rounds with KCH pediatric admission outcome data. We then calculated the case detection rate as the proportion of all childhood deaths in the KHDSS area that were captured at KCH during the study period:

$$CDR = \frac{\text{No. KHDSS-resident children who died at KCH}}{\text{Total no. childhood deaths among KHDSS residents}}$$

Using Verbal Autopsy

A better approach to estimating the sensitivity of hospital-based surveillance is to use *disease specific* mortality data to calculate the proportion of childhood TB deaths captured by the study. Poor quality vital registration data in Kilifi District make these data unsuitable for this

analysis. We therefore made use of data from an ongoing verbal autopsy (VA) study within the KHDSS.

Details of the Kilifi verbal autopsy study, including validation of the methodology using hospital records of the cause of death, have been published elsewhere (*10*). Deaths among KHDSS residents are identified by the thrice yearly enumeration rounds, and relatives of the deceased are then visited at home as soon as possible after the locally accepted 1 month bereavement period. Following consent, verbal autopsy is performed using the WHO Sample Vital Registration with Verbal Autopsy (SAVVY) tool. Structured questionnaires include an initial narrative section with open questions about the circumstances of death, followed by a series of closed questions that provide detailed information about the medical history and associated clinical features. Two independent clinicians then code the causes of death in each case according to a standard rubric and the WHO International Statistical Classification of Diseases Version 10 (ICD10). In the case of a discrepancy between the two clinicians, a third clinician reviews the case blind to adjudicate, and if there is no agreement between the three reviewers they meet to discuss the case to form a consensus.

Using each child's unique KHDSS personal identification (PID) number we merged VA and KIDS TB records to calculate the proportion of TB deaths among KHDSS resident children with that were captured by the KIDS TB study. We defined TB deaths as those whose cause was coded as TB or which occurred in a patient with documented tuberculosis according to the respondent and/or any available supporting documentation, including death certificates, burial permits and post mortem reports.

We then estimated the case detection rate as

$$CDR = \frac{\text{No. TB deaths in VA study that occurred in children captured by KIDS TB Study}}{\text{No. TB deaths in VA study}}$$

Although the true mortality burden of TB among children in Kilifi District was not known, we predicted that the number of child TB cases diagnosed by VA was likely to be small (since TB is responsible for a minority of childhood deaths and is even more difficult to diagnose retrospectively by VA than in clinical practice); and that the precision of our case detection rate estimate was therefore likely to be poor.

To mitigate this, we also used the VA study to identify the much larger group of children whose reported clinical features before death met the KIDS TB Study criteria for suspected TB. Healthcare-seeking behavior in Kilifi is usually determined by the clinical features of an illness, rather than the diagnosis per se (*11*,*12*). We reasoned, therefore, that of all children with clinical features of suspected TB who died, the proportion captured by the KIDS TB Study would provide a surrogate measure of the case detection rate:

$$CDR = \frac{\text{No. TB suspect deaths in VA study that were captured by KIDS TB Study}}{\text{No. TB suspect deaths in VA study}}$$

For the purposes of this analysis we defined '*pneumonia not responding to first line antibiotics*' as death due to pneumonia despite reported treatment.

Risk Factors for Childhood TB

We summarized the distribution among cases and controls of each putative risk factor, and derived crude odds ratios (OR) and 95% confidence intervals (CI) in each case. Likelihood ratio tests for a general association were performed and p values reported.

To explore associations with TB contact variables we used children with no TB contact as the baseline group for comparison. Since some children had a history of more than one TB contact, we assumed an individual child had an equal probability of acquiring TB from each contact; created a separate record for each child-contact pair; and weighted each of these pairs in the analysis by the reciprocal of the number of TB contacts reported for each child.

We then derived multivariable logistic regression models to identify independent risk factors for TB. Categorical variables with at least a weak association with TB in the univariable analysis (likelihood ratio test p value ≤ 0.1) were included in the model. We performed backward stepwise logistic regression using standard selection criteria, such that variables that were not significantly associated with TB (Wald p value <0.5) were sequentially dropped from the model. Likelihood ratio tests were used to test for potential interactions in the final model. Based on this model adjusted odds ratios and 95% confidence intervals were derived for the associations with TB of each variable included; p values for each association were derived using the Wald test.

We estimated the population attributable fraction (PAF) of childhood TB due to close contact with a known case of adult TB. We confined this analysis to children under 5 years for two reasons. First, it is well documented from natural history studies in the pre-chemotherapy era that >90% active TB disease in this age group occurs within 2 years of infection (*13*). The number of contacts identified during the 2 year recruitment period therefore provides a good estimate of the likely number of contacts putting children at risk, since the overall rate of TB notifications in the study population is constant. Second, this is the group targeted for isoniazid chemoprophylaxis since they are the most vulnerable (*1*).

We multiplied the number of notified KHDSS-resident TB cases among adults (TB_{khdss}) by the mean number of child household contacts under 5 years old per TB case ($\bar{C}_{household}$) to estimate the number of KHDSS-resident children with a known household TB contact ($N_{contacts}$) during this study period:

$$N_{contacts} = TB_{khdss} \times \bar{C}_{household}.$$

We then estimated the number of person years observation among children <5 years old with a known household TB contact ($pyo_{contacts}$) as

$$pyo_{contacts} = N_{contacts} \times 2years.$$

We calculated the incidence of TB among children <5 years old with and without a history of household TB contact as

$$I_{contacts} = \frac{tb_{contacts}}{pyo_{contacts}} \text{ and } I_{non-contacts} = \frac{tb_{non-contacts}}{pyo_{total} - pyo_{contacts}},$$

where $tb_{contacts}$ and $tb_{non\text{-}contacts}$ are the numbers of TB cases among children <5 years old with and without a known history of TB contact, and pyo_{khdss} is the total person years observation among children <5 years old resident in the KHDSS. The Incident Rate Ratio (*IRR*) was then calculated as

$$IRR = \frac{I_{contacts}}{I_{non-contacts}}$$

The community prevalence of household TB contact (p) among KHDSS-resident children <5 years old during the 2 year study period was calculated as

$$p = \frac{N_{contacts}}{N_{total}} = \frac{pyo_{contacts}}{pyo_{total}}$$

Finally we calculated the PAF for contact with a notified adult case of TB as

$$PAF = \frac{p(IRR - 1)}{p(IRR - 1) + 1}$$

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Technical Appendix Table 1. Symptoms and signs of possible TB

Symptoms of possible TB	Signs of possible TB
Any of the following: • fever, night sweats, weight loss, lethargy, or failure to thrive; • cough or dyspnoea; • chest infection not responding to appropriate first line antibiotics; • abdominal pain or swelling; • change in temperament or conscious level, or convulsions; • new or progressive spinal or joint deformity	Any of the following: • fever, wasting, lymphadenopathy; • cough, tachypnoea, signs of respiratory distress; • focal chest signs (e.g., bronchial breathing, crackles, wheeze, pleural rub, signs of pleural effusion); • signs of pericardial effusion and/or congestive cardiac failure; • abdominal mass, hepatomegaly, splenomegaly or ascites; • lethargy, decreased conscious level, signs of meningism (photophobia,neck stiffness, Kernig's sign) or convulsions; • spinal gibbus or enlarged non-tender joint; • signs of tuberculin hypersensitivity (e.g., erythema nodosum, phlyctenular conjunctivitis)

Technical Appendix Table 2. Case definitions

Confirmed TB • Disease at any site: Identification of M. tuberculosis complex (MTBC) from clinical specimens by culture or Xpert MTB/RIF assay, in the appropriate clinical context
Highly probable TB • Disease at any site: positive microscopy for acid fast bacilli (AFB) but negative mycobacterial culture/PCR of clinical specimens in the appropriate clinical context; • Disease at any site: histology of biopsy tissue showing caseating granulomata; • Intra-thoracic TB: CXR appearances highly suggestive of active TB: — non-pyogenic pleural effusion with no evidence of alternative cause — cavitation associated with subacute/chronic pneumonia and no other identified cause of cavitation (e.g., Klebsiella or Staphylococcal sepsis) — hilar/mediastinal lymph nodes plus a positive TST and no other identified cause; • Miliary TB: miliary shadowing on CXR in an HIV un-infected child; • TB Meningitis (TBM): clinical features of meningitis with CSF changes consistent with TBM (predominantly lymphocytic cellular infiltrate, protein concentration >0.8g/l, glucose concentration <2.2mmol/l, and no established alternative diagnosis); • TB Lymphadenitis: cervical lymphadenopathy plus sinus formation or a positive TST; • Abdominal TB: abdominal mass or ascites, with abdominal lymphadenopathy on ultrasound; • Spinal TB: spinal gibbus in the absence of another obvious cause; • Hypersensitivity reactions: erythema nodosum or phlyctenular conjunctivitis with chest radiograph evidence of primary TB
Confirmed or highly probable TB (CHPTB) • Children who met the case definition for 'Confirmed TB' or 'Highly Probable TB'
Possible TB • Children treated for TB, but who did not meet the case definition for either 'Confirmed TB' or 'Highly Probable TB'
All TB cases • All children with 'Confirmed TB', 'Highly Probable TB', or 'Possible TB'
Not TB (TB confidently excluded) • All clinical features explained by a definitive alternative diagnosis, making TB highly unlikely; and/or insufficient clinical indication for a trial of TB treatment and no clinical deterioration during follow up in the absence of TB therapy
Not classifiable • Children who did not meet criteria for confirmed, highly probable or possible TB, and in whom TB could not confidently be excluded, for example because they died or were lost to follow up

Technical Appendix Table 3. Estimated annual national case burden and incidence of childhood TB by age group (2010)

Age group	Child TB cases in the KHDSS (tb_{khdss})*	Ratio of child to adult cases in KHDSS (*r*)†	Child TB cases in Kenya (tb_{kenya})†	Kenya population (millions) (*14*)	Incidence per 100,000/y
0–4 y	86	86/678	11,401	6.2	184
5–9 y	31	31/678	4,110	6.0	69
10–14 y	9	9/678	1,193	5.4	22
<15 y	126	126/678	16,704	17.6	95

*tb_{khdss}, No. confirmed and highly probable TB cases after adjustment for the case detection rate
†*r*, Ratio of cases in age group to the total number of notified adult cases in the KHDSS (678)
‡tb_{kenya}, No. child TB cases in Kenya, estimated by multiplying number of notified adult cases in Kenya (89,883) by ratio (*r*) of child to adult cases in KHDSS.

Technical Appendix Table 4. Association of TB contact history with confirmed or highly probable TB among children investigated for TB at KCH and CPGH (Aug 2009–Jul 2011)

Characteristic	TB cases	Controls	Odds ratio for TB (95% CI)		p value
History of close TB contact					<0.0001
No history of close TB contact	87	1,074	1.0	(-)	
Any history of close TB contact	63	159	5.0	(3.4–7.3)	
Proximity of TB contact*					<0.0001
Contact outside the household	5	40	1.5	(0.6–4.0)	
Contact sleeps in same household	12	39	3.8	(1.9–7.5)	
Contact sleeps in same room	46	80	7.1	(4.6–10.8)	
Smear status of TB contact*					<0.0001
Smear negative	19	60	3.9	(2.2–6.8)	
Smear positive	38	70	6.7	(4.3–10.5)	
Smear status unknown	6	29	2.6	(1.0–6.3)	
Relationship of contact to child*†					<0.0001
Parent	40	75	6.6	(4.2–10.3)	
Grandparent	4	24	2.3	(0.8–6.7)	
Aunt or uncle	12	38	4.1	(2.0–8.3)	
Sibling	3	7	4.7	(1.1–20.8)	
Other	6	21	3.6	(1.4–9.3)	
No. close TB contacts*					<0.0001
1 close TB contact	58	147	4.9	(3.3–7.1)	
≥1 close TB contact	5	12	5.1	(1.8–14.9)	

*Compared with children who had no history of TB contact.
†Actual numbers of children presented, but weighted analysis used to derive odds ratios (see methods).

Technical Appendix Table 5. Population attributable fraction for a known household TB contact among KHDSS-resident children <5 y old (Aug 2009–Jul 2011)

Variable	Calculation
Numerators	
No. KHDSS-resident TB cases <5 y old with a known TB contact	$tb_{contacts} = 15$
No. KHDSS-resident TB cases <5 y old with no known TB contact	$tb_{non\text{-}contacts} = 15$
Denominators	
No. TB cases among KHDSS resident adults	$TB_{khdss} = 678$
Mean no. household contacts <5 y old per TB case	$\bar{C}_{household} = 362/195$
No. KHDSS resident contacts <5 y old of known TB cases	$N_{contacts} = TB_{khdss} \times \bar{C}_{household} = 1{,}259$
Person years observation among all KHDSS-resident children <5 y	$pyo_{total} = 89{,}503$
Person years observation among KHDSS-resident TB contacts <5 y	$pyo_{contacts} = N_{contacts} \times 2yrs = 2{,}518$
Incidence rates (per 100,000/year)	
TB incidence among child contacts of known TB cases	$I_{contacts} = \frac{tb_{contacts}}{pyo_{contacts}} = 596$
TB incidence among children with no known TB contact	$I_{non-contacts} = \frac{tb_{non-contacts}}{pyo_{total} - pyo_{contacts}} = 17$
Incidence rate ratio	$IRR = \frac{I_{contacts}}{I_{non-contacts}} = 35.1$
TB contact prevalence	
Prevalence of known TB contact among KHDSS-resident children <5 y	$p = \frac{N_{contacts}}{N_{total}} \equiv \frac{pyo_{contacts}}{pyo_{total}} = \frac{2{,}518}{89{,}503} = 2.8\%$
Population attributable fraction	
Population attributable fraction for a known TB contact	$PAF = \frac{p(IRR-1)}{p(IRR-1)+1} = 49\%$